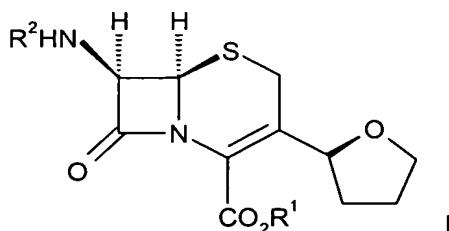


CLAIMS

1. A process for preparing a 3-cyclic-ether-substituted cephalosporin of the formula I:



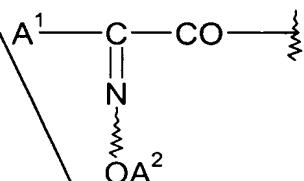
*Sub
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5 or a pharmaceutically acceptable salt thereof,

wherein

the group CO_2R^1 is a carboxylic acid or a carboxylate salt; and

R^2 has the formula:



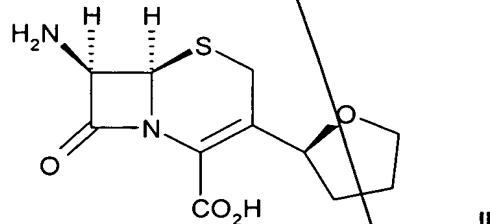
10 wherein

A^1 is selected from the group consisting of $\text{C}_{6-10}\text{aryl}$, $\text{C}_{1-10}\text{heteroaryl}$ and $\text{C}_{1-10}\text{heterocyclyl}$;

A^2 is selected from the group consisting of hydrogen, $\text{C}_{1-6}\text{alkyl}$, $\text{C}_{3-10}\text{cycloalkyl}$, $\text{C}_{6-10}\text{aryl}$, $\text{C}_{1-6}\text{alkyl}(\text{CO})(\text{C}_{1-6})\text{alkyl-O-}$, $\text{HO}(\text{CO})(\text{C}_{1-6})\text{alkyl}$, mono-($\text{C}_{6-10}\text{aryl}$)($\text{C}_{1-6}\text{alkyl}$),

15 di-($\text{C}_{6-10}\text{aryl}$)($\text{C}_{1-6}\text{alkyl}$), and tri-($\text{C}_{6-10}\text{aryl}$)($\text{C}_{1-6}\text{alkyl}$);

comprising reacting a compound of formula II:



with a compound of the formula III:



20 wherein

R^2 is as defined above; and

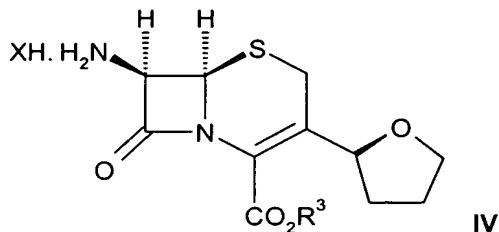
L is selected from the group consisting of hydroxy, halo, azido, mono($\text{C}_{1-6}\text{alkyl}$)carbonate, ($\text{C}_{1-6}\text{alkyl}$)carboxylate, ($\text{C}_{6-10}\text{aryl}$)carboxylate,

Su
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mono-(C₆₋₁₀aryl)(C₁₋₆alkyl)carboxylate,
di(C₁₋₆alkyl)phosphorothioate, (C₁₋₆alkyl)sulfonyl, mono-(C₁₋₆alkyl)(C₆₋₁₀aryl)sulfonyl,
di-(C₁₋₆alkyl)(C₆₋₁₀aryl)sulfonyl, (C₁₋₆alkyl)-(CO)-S-, cyano-C₁₋₆alkoxy, C₆₋₁₀aryloxy,
3-benzthiazolyloxy, 8-quinolinyloxy and N-oxy-succinimidyl;

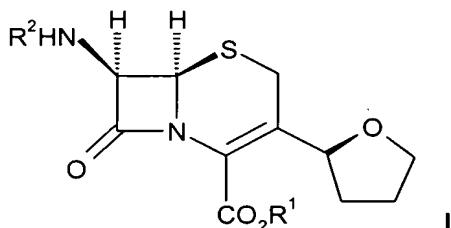
- 5 in the presence of a solvent, a base, an optional coupling agent and an optional catalyst.

2. The process according to claim 1 further comprising the step of preparing said compound of formula II by reacting a compound of formula IV:

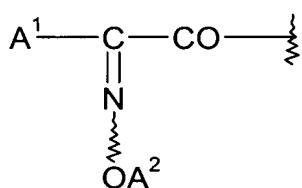


- 10 wherein R³ is para-nitrobenzyl or allyl; and X is halo;
with a suitable deprotecting agent; in the presence of a solvent.

3. A process for preparing a 3-cyclic-ether-substituted cephalosporin of the formula I:

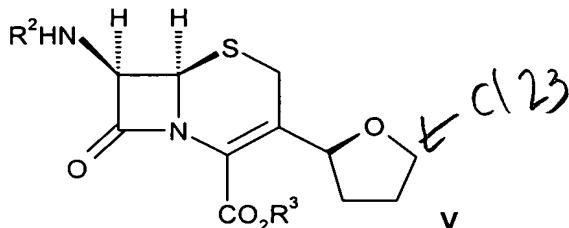


- 15 or a pharmaceutically acceptable salt thereof,
wherein the group CO₂R¹ is a carboxylic acid or a carboxylate salt; and
R² has the formula:



- 20 wherein A¹ is selected from the group consisting of C₆₋₁₀aryl, C₁₋₁₀heteroaryl and
C₁₋₁₀heterocyclyl;
A² is selected from the group consisting of hydrogen, C₁₋₆alkyl, C₃₋₁₀cycloalkyl,
C₆₋₁₀aryl, C₁₋₆alkyl(CO)(C₁₋₆)alkyl-O-, HO(CO)(C₁₋₆)alkyl, mono-(C₆₋₁₀aryl)(C₁₋₆alkyl),
di-(C₆₋₁₀aryl)(C₁₋₆alkyl) and tri-(C₆₋₁₀aryl)(C₁₋₆alkyl);

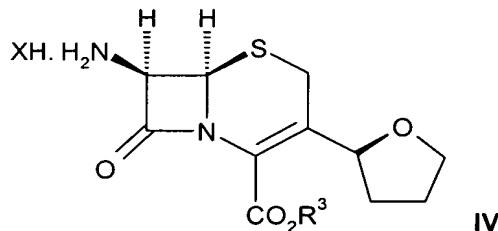
comprising reacting a compound of formula V:



wherein R^2 is as defined above; and R^3 is para-nitrobenzyl or allyl;

with a suitable deprotecting agent in the presence of a solvent.

- 5 4. The process according to claim 3 further comprising preparing said compound of formula V by reacting a compound of formula IV:

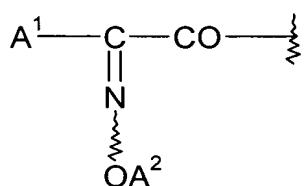


wherein R^3 is para-nitrobenzyl or allyl; and X is halo;

with a compound of the formula III:

- 10 R^2L III;

wherein R^2 has the formula:



wherein A^1 is selected from the group consisting of C_{6-10} aryl, C_{1-10} heteroaryl and C_{1-10} heterocyclyl;

- 15 A^2 is selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-10} cycloalkyl, C_{6-10} aryl, C_{1-6} alkyl(CO)(C_{1-6})alkyl-O-, HO(CO)(C_{1-6})alkyl, mono-(C_{6-10} aryl)(C_{1-6} alkyl), di-(C_{6-10} aryl)(C_{1-6} alkyl) and tri-(C_{6-10} aryl)(C_{1-6} alkyl); and

- 20 L is selected from the group consisting of hydroxy, halo, azido, mono(C_{1-6} alkyl)carbonate, (C_{1-6} alkyl)carboxylate, (C_{6-10} aryl)carboxylate, mono-(C_{6-10} aryl)(C_{1-6} alkyl)carboxylate, di(C_{1-6} alkyl)phosphorothioate, (C_{1-6} alkyl)sulfonyl, mono-(C_{1-6} alkyl)(C_{6-10} aryl)sulfonyl, di(C_{1-6} alkyl)(C_{6-10} aryl)sulfonyl, (C_{1-6} alkyl)-(CO)-S-, cyano- C_{1-6} alkoxy, C_{6-10} aryloxy, 3-benzthiazolyloxy, 8-quinolinylloxy and N-oxy-succinimidyl;

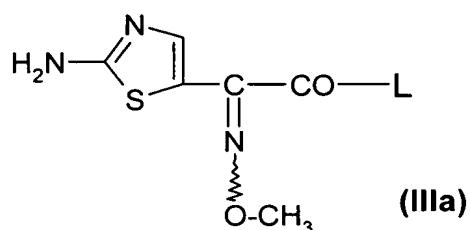
in the presence of a solvent.

5. The process according to claim 1, wherein said A¹ moiety of said R² is C₁₋₁₀heteroaryl selected from the group consisting of furyl, thienyl, pyridyl, aminothiazolyl and aminothiadiazolyl, wherein said amino moiety of said aminothiazolyl or aminothiadiazolyl is 5 optionally protected.

6. A process according to claim 1, wherein said A² moiety of said R² is C₁₋₆alkyl.

7. A process according to claim 1, wherein L of said compound of the formula III is selected from the group consisting of halo, methanesulfonyl, diethylphosphorothioate and 3-benzthiazolyloxy.

10 8. A process according to claim 1, wherein said compound of formula III has a formula IIIa:



and wherein L is selected from the group consisting of halo, methanesulfonyl, diethylphosphorothioate and 3-benzthiazolyloxy.

15 9. A process according to claim 1, wherein said solvent is water, acetone, tetrahydrofuran, ethyl acetate, dimethylacetamide, dimethylformamide, acetonitrile, methylene chloride, 1,2-dichloroethane or mixtures thereof.

10. A process according to claim 1, wherein said solvent is water, acetone, or mixtures thereof.

20 11. A process according to claim 1, wherein a catalyst is used.

12. A process according to claim 11 wherein said catalyst is a Lewis acid catalyst selected from the group consisting of boron trihalide and aluminum halide.

13. A process according to claim 1 wherein said base is diisopropylethylamine or sodium hydroxide.

25 14. A process according to claim 1, wherein said coupling agent is selected from the group consisting of N,N'-diethylcarbodiimide, N,N'-dipropyl carbodiimide, N,N'-diisopropylcarbodiimide, N,N'-dicyclohexylcarbodiimide, N-ethyl-N'-(3-(dimethylamino)propyl)carbodiimide, N,N'-carbonyldiimidazole and N,N'-carbonyldithiazole.

30 15. A process according to claim 1, wherein said coupling agent is N,N'-dicyclohexylcarbodiimide.

16. A process according to claim 1, wherein said X is chloro.

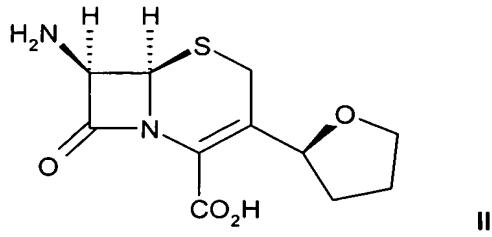
17. A process according to claim 2, wherein said R^3 is para-nitrobenzyl and said suitable deprotecting agent is sodium dithionite or a catalytic hydrogenating agent.

18. A process according to claim 2, wherein said R^3 is allyl and said suitable deprotecting agent is tetrakis triphenylphosphine palladium (0).

5 19. A process according to claim 17, wherein said solvent is acetone, water, tetrahydrofuran or mixtures thereof.

20. A process according to claim 4, wherein said solvent is methylene chloride, tetrahydrofuran or mixtures thereof.

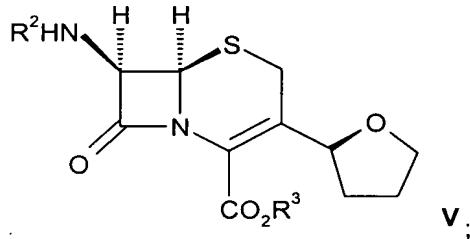
21. A compound of formula II:



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22. The compound according to claim 21 wherein said compound of the formula II has an enantiomeric or diastereomeric purity of 96% to 100%.

23. A compound of formula V:



15 15. wherein R^2 is acyl; and R^3 is para-nitrobenzyl or allyl.

24. The compound according to claim 23 wherein said compound of the formula V has an enantiomeric or diastereomeric purity of 96% to 100%.